Subcortical volumetric changes across the adult lifespan: subregional thalamic atrophy accounts for age-related sensorimotor performance declines

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Abstract

Even though declines in sensorimotor performance during healthy aging have been documented extensively, its underlying neural mechanisms remain unclear. Here, we explored whether age-related subcortical atrophy plays a role in sensorimotor performance declines, and particularly during bimanual manipulative performance (Purdue Pegboard Test). The thalamus, putamen, caudate and pallidum of 91 participants across the adult lifespan (ages 20 – 79 years) were automatically segmented. In addition to studying age-related changes in the global volume of each subcortical structure, local deformations within these structures, indicative of subregional volume changes, were assessed by means of recently developed shape analyses. Results showed widespread age-related global and subregional atrophy, as well as some notable subregional expansion. Even though global atrophy failed to explain the observed performance declines with aging, shape analyses indicated that atrophy in left and right thalamic subregions, specifically subserving connectivity with the premotor, primary motor and somatosensory cortical areas, mediated the relation between aging and performance decline. It is concluded that subregional volume assessment by means of shape analyses offers a sensitive tool with high anatomical resolution in the search for specific age-related associations between brain structure and behavior.

Keywords

Aging; Coordination; Thalamus; Shape; Mediation

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1. Introduction

Bimanual skills are ubiquitous during many daily life activities, such as getting dressed or eating. During healthy aging, these skills have been shown to deteriorate (Bernard & Seidler, 2012; Fling & Seidler, 2012; Marneweck, Loftus, & Hammond, 2011; Serbruyns et al., 2015; Sullivan et al., 2001; Swinnen et al., 1998). However, fundamental knowledge of the neural mechanisms behind these age-related declines is rather limited.

Recent aging studies have focused on activity of the cerebral cortex, and have made some progress in determining the role of age-related functional brain changes in bimanual performance declines (Goble et al., 2010; Heitger et al., 2013; Kiyama, Kunimi, Iidaka, & Nakai, 2014; Solesio-Jofre et al., 2014). Other aging studies have demonstrated a significant role of microstructural changes in white matter structures and particularly the corpus callosum (Fling et al., 2011; Gooijers & Swinnen, 2014; Serbruyns et al., 2015; Sullivan et al., 2001), the largest white matter tract connecting interhemispheric cortical regions (Jarbo, Verstynen, & Schneider, 2012). However, to the best of our knowledge, the role of subcortical changes in bimanual performance declines in healthy aging has not been investigated. The importance of subcortical structures for bimanual coordination is indirectly implied by several functional magnetic resonance imaging (fMRI) studies in healthy young adults showing that bimanual coordination relies on a distributed network, including subcortical structures (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003, 2004a, 2004b; Kraft et al., 2007; Ng, Sowman, Brock, & Johnson, 2013; Puttemans, Wenderoth, & Swinnen, 2005; Van Der Graaf, De Jong, Maguire, Meiners, & Leenders, 2004). Furthermore, patients with subcortical impairments, such as patients with Parkinson's disease or with subcortical lesions, have been shown to experience difficulties with bimanual performance (Haaxma et al., 1995; Johnson et al., 1998; Kuoppamaki et al., 2005; Mochizuki-Kawai et al., 2004; Serrien, Steyvers, Debaere, Stelmach, & Swinnen, 2000; Swinnen, Steyvers, Van Den Bergh, & Stelmach, 2000; Verschueren, Swinnen, Dom, & De Weerdt, 1997). Based on previous indications that subcortical gray matter structures undergo age-related degenerative changes (Cherubini, Peran, Caltagirone, Sabatini, & Spalletta, 2009; Fjell et al., 2013; Goodro, Sameti, Patenaude, & Fein, 2012; Gunning-Dixon, Head, McQuain, Acker, & Raz, 1998; Hughes et al., 2012; Inano et al., 2013; Jancke, Merillat, Liem, & Hanggi, 2014; Jiang et al., 2014; Li et al., 2014; Long et al., 2012; Walhovd et al., 2005; Walhovd et al., 2011), investigating the relationship between these changes and bimanual functioning may help in unraveling the neural basis of age-related bimanual performance declines.

The main subcortical structures involved in bimanual coordination are the thalamus (Debaere et al., 2003, 2004a, 2004b; Ng et al., 2013), putamen (Debaere et al., 2003, 2004b; Ng et al., 2013; Van Der Graaf et al., 2004), caudate (Debaere et al., 2003; Ng et al., 2013) and pallidum (Debaere et al., 2004a, 2004b; Ng et al., 2013; Van Der Graaf et al., 2004). These structures are part of the cortico-subcortical

motor circuit, receiving inputs from the cerebral cortex via cortico-striatal inputs and ultimately projecting back to distinct zones of the cortex through thalamocortical pathways (Alexander, Delong, & Strick, 1986; Hoover & Strick, 1993). Anatomical connectivity information, derived from diffusion tensor imaging (DTI) and probabilistic tractography, has shown that these subcortical projections are topographically organized, i.e., clustered according to function, congruent with primate data. In this way, each of these subcortical structures can be parcellated into functionally distinct subregions (Behrens et al., 2003; Tziortzi et al., 2014; Zhang, Snyder, Shimony, Fox, & Raichle, 2010). Recently, a new method has been proposed that, in addition to the assessment of total volume per subcortical structure (i.e., 'global' volumes), allows for accurate and robust localization of volumetric changes within such distinct subregions of each of these structures (i.e., 'subregional volume') by means of shape analyses in T1-weigthed MRI images (Patenaude, Smith, Kennedy, & Jenkinson, 2011). That is, it allows for the detection of shape differences in terms of inward or outward deformation, which implies local volume decreases (i.e., subregional atrophy) or local volume increases (i.e., subregional expansion), respectively. Previous research from our group in traumatic brain injury patients and healthy controls has shown that these subregional volumetric measures provide greater sensitivity as compared to global volumetric measures in detecting correlations with behavioral measures (Leunissen et al., 2014). Moreover, shape analyses enable purely local volumetric analyses, which are based directly on the location of the structures' boundaries and thus are not dependent on tissue-type classification or smoothing extents (Patenaude et al., 2011). As such, shape analyses have the potential to be more sensitive to local volumetric changes as compared to more conventional methods. This idea is further strengthened by two very recent studies detecting gray matter subcortical differences between patients and healthy controls using shape analyses, but not (Menke et al., 2014) or to a lesser extent (Kim, Kim, Seo, Suh, & Koh, 2013) using voxel-based morphometry. Furthermore, shape analyses have already been employed successfully to detect atrophy with increasing age in subregions of the bilateral thalamus (Hughes et al., 2012; Jiang et al., 2014), bilateral putamen, and left pallidum (Jiang et al., 2014). In view of the observed functional topography within subcortical structures, shape analyses offer great potential for the identification of age-related atrophy in subcortical subregions potentially mediating sensorimotor performance declines.

In the current study, we investigated the role of global and subregional subcortical volumetric changes in age-related bimanual performance declines across the adult lifespan. Bilateral thalamus, putamen, caudate and pallidum were selected as structures of interest. Our hypotheses were three-fold: (1) bimanual performance will decline with increasing age, (2) the selected subcortical structures will show atrophy with increasing age, and (3) atrophy of subregions connected with cortical regions involved in motor coordination will account for age-related bimanual performance declines.

To the best of our knowledge, this is the first study offering a detailed overview of age-related global and in particular subregional volumetric changes in multiple subcortical structures across the whole adult lifespan, as well as in delineating their role in sensorimotor performance declines.

2. Materials and Methods

2.1 Participants

Participants within an age range of 20 to 79 years old were recruited from the general population by means of advertisements and active recruitment. Participants with current or previous psychiatric illness, neurological illness, use of anti-epileptic medication, or drug or alcohol abuse were excluded, as were participants with diabetes, contraindication to MRI, impaired hand function, or highly trained bimanual function (e.g., musicians). Additionally, exclusion criteria included a score below 26/30 on the Montreal Cognitive Assessment scale for participants aged 60 and older (Nasreddine et al., 2005). After additionally excluding 1 participant due to detection of a cyst, the final sample consisted of 91 participants (46 males, mean age ± SEM: 49.59 ± 1.86 years). All participants were right-handed, as verified by the Edinburgh Handedness Inventory (laterality quotient, mean ± SEM: 95.23 ± 1.14), and had normal or corrected to normal vision. Prior to giving written consent, all participants were fully informed about the experimental procedures. The study received approval from the local Ethics Committee for Biomedical Research at KU Leuven and was performed in accordance with the 1964 Declaration of Helsinki and its amendments.

2.2 Bimanual Purdue Pegboard Test

The Purdue Pegboard Test (Lafayette instrument company, USA) is a widely known clinical measure of fine finger manipulation speed. It consists of manipulating a maximum number of small pins in two vertical columns with pinholes on a board, within a 30-sec time period (Desrosiers, Hebert, Bravo, & Dutil, 1995; Tiffin & Asher, 1948). The test was performed three times with both hands simultaneously. Before starting, the participants were allowed to practice with 4 pairs of pins. The dependent variable was the average number of pairs inserted during the three trials. Outlier detection was performed by transforming the data into z-scores. A trial was considered an outlier when the absolute value of z was above 3.

2.3 Image acquisition

A Siemens 3T Magnetom Trio magnetic resonance imaging (MRI) scanner (Siemens, Erlangen, Germany) with a 12-channel matrix head coil was used for acquisition of a 3D magnetization prepared rapid gradient echo (MPRAGE) high resolution T1-weighted anatomical image (repetition time = 2300 msec; echo time = 2.98 msec; 1 x 1 x 1.1 mm^3 voxels; field of view = 240 x 256 mm^2; 160 sagittal slices, flip angle 9°).

2.4 Image processing

All images were manually checked for the presence of anatomical abnormalities or MR artifacts using xjView software in MATLAB 7.12 (The MathWorks Inc., Natick, MA, 2011). Automatic segmentation of the subcortical structures (left and right: thalamus, putamen, caudate and pallidum, see Figure 1) from each participant's anatomical image was conducted with FMRIB's Integrated Registration Segmentation Toolkit (FSL FIRST; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST). FSL FIRST (desribed in detail by Patenaude et al., 2011) incorporates both intra- and interstructural variability to perform the segmentations. A surface mesh is created for each subcortical structure by fitting models of deformable meshes, constructed from a training set of 336 manually labeled anatomical images. These deformable meshes consist of sets of vertices connected by edges and are topologically equivalent to a tessellated sphere. Moreover, FSL FIRST maximizes the posterior probability of the shape of the subcortical structures by searching through linear combinations of shape modes of variation given the observed intensities in the anatomical image. In the current study, the meshes were reconstructed in the native space of the model (i.e., MNI space). Next, pose (global rotation and translation) was removed from the meshes by a rigid alignment with 6 degrees of freedom and boundary correction was applied. Segmentations were visually inspected for all participants in sagittal, coronal, and axial views using the FSLVIEW toolbox.

2.5 Age-related subcortical volumetric changes

2.5.1 Global volumetric changes

For each structure, the global volume measurement (i.e., of the entire structure) was extracted from the outputs of the FSL FIRST segmentation and was imported into the Statistical Package for the Social Sciences (SPSS, version 22.0). Total intracranial volume (TIV) was obtained in SPM8 (new segment toolbox) by adding the volumes of white matter, gray matter and cerebrospinal fluid together. Next, the global volume was corrected for individual variation in brain size using the following formula: *corrected global volume = global volume (mm^3)/TIV (mm^3) * 1000*. The corrected global volumes were used for further analyses. Pearson correlation analyses were used to explore the effect of age on corrected global volume of the different subcortical structures across all participants.

2.5.2 Shape analyses: subregional volumetric changes

Differences in the shape of a subcortical structure can be caused by inward deformations, indicative of local volume decreases (subregional atrophy), and/or outward deformations, indicative of local volume increases (subregional expansion). By revealing the exact location of these volumetric changes within

a structure, shape analyses can offer more detailed insights into age-related subcortical changes as compared to global volume analyses. FSL FIRST shape analyses (Patenaude et al., 2011) use the deformable model approach as described above, to restrict topology of the structures and to preserve inter-subject vertex correspondence, such that vertex-wise comparisons across individuals or between groups can be performed. More specifically, vertex locations from each participant are projected onto the surface normal (i.e., perpendicular to the tangent plane to the surface and outward pointing) of the average shape of this particular cohort. These vertices represent the signed, perpendicular distance from the average surface. Negative values reflect inward movement of the vertices (subregional volume decreases), positive values reflect outward movement of the vertices (subregional volume increases). We employed vertex-wise statistics to investigate subregional age-related volumetric differences of the subcortical structures. With the aim of offering a detailed overview of these differences across the lifespan, we compared the subcortical shapes of participants of each of the last 5 decades of the age range in this study (i.e., the 4th, 5th, 6th, 7th and 8th decade, including participants between 30-39, 40-49, 50-59, 60-69 and 70-79 years, respectively) to the shapes of the youngest decade in our sample (i.e., the 3rd decade, including participants between 20-29 years) (Table 1). On this account, a general linear model (GLM) approach, as implemented in FSL, was employed to perform two-sample *t*-tests with Threshold-Free Cluster Enhancement correction for multiple comparisons (Smith & Nichols, 2009). Results were rendered on the shape surface using ParaView 4.1.0, providing a map of the subcortical subregional differences.

2.6 Age-related changes in bimanual performance

To investigate age-related changes in bimanual performance across the adult lifespan, we calculated the correlation strength between age and average number of pairs inserted during the bimanual version of the Purdue Pegboard Test using Pearson correlation analyses.

2.7 Relation between age-related subcortical atrophy and bimanual performance decline

We employed mediation analyses (explained in more detail below) to investigate whether age-related declines in bimanual performance could be explained by atrophy of the subcortical structures. A first criterion for mediation to occur is that there is an effect of the mediator (here: global or subregional subcortical volume) on the dependent variable (here: bimanual performance), which remains significant after controlling for the effect of the independent variable (here: age). Accordingly, before performing the mediation models, we explored which structures (based on corrected global volume) and/or subregions of structures (based on subregional volume) met this criterion, and these were selected as potential mediators. An overview of this step can be found in Figure 2 (Step 1).

2.7.1 Selection of potentially mediating structures based on global volume

Potential relations between bimanual performance and global volume of the subcortical structures, independent of the effect of age on performance, were determined by calculating partial Pearson correlations. Structures showing a significant partial correlation were selected as potentially mediating structures.

2.7.2 Selection of potentially mediating subregions based on subregional volume

Additionally, we investigated whether shape analyses could provide greater sensitivity in detecting correlations with behavior. On this account, the GLM (FSL) was used to correlate subregional volume of the subcortical structures with bimanual performance, controlling for the effect of age. As a precaution against false-positive results, only clusters with an extent of ≥ 10 voxels and significant at $p \leq 0.005$ (uncorrected) were selected as potentially mediating subregions. The outputs of the partial correlation analyses were binarized (i.e., the voxel values within a significant cluster were set to one, and otherwise to zero), and next these binary images served as a mask to extract the mean vertex value per significant cluster, indicative of subregional volume.

2.7.3 Mediation analyses

After selection of the potential global and subregional volume mediators, PROCESS, a SPSS macro recently developed by Hayes (2012), was used to run the mediation models (see Figure 2, Step 2). First, the total effect of age on bimanual performance *(c)* was estimated by regressing age on performance without any mediators in the model. Next, using ordinary least squares path analysis, age was modeled to affect performance directly, as well as indirectly through the potential global and/or subregional volume mediators assumed to be causally located between age and performance. As depicted in the mediation models in Figure 2 (Step 2), the direct effect of age on performance is estimated with *c'*, and the indirect effect is estimated as *a*b*, that is the product of the effect of age on global or subregional volume *(a)* and the effect of global or subregional volume on bimanual performance, controlling for age *(b)*. The indirect effect was evaluated using 10000 stratified bootstrap samples to determine a 95% bias-corrected confidence interval. The sum of the direct and indirect effect equals the total effect of age on performance *(c)*. Finally, R^2_{med} represents the proportion of variance in bimanual performance, attributable to the indirect effect of age on bimanual performance through the potential global or subregional volume mediators.

2.8 Statistical analyses

Unless otherwise stated, an *alpha* level of .05 was used for statistical analyses, and correction for multiple comparisons was applied using Bonferroni correction (Olejnik, Li, Supattathum, & Huberty, 1997). Only results surviving correction for multiple comparisons are reported.

3. Results

3.1 Age-related subcortical volumetric changes

3.1.1 Global volumetric changes

Descriptive statistics of uncorrected global volumes, global volumes corrected for total intracranial volume, and Pearson correlations of corrected global volumes with age are reported in Table 2. There was a significant negative correlation between age and corrected global volume in all structures (all *p*-values < .001), except the left and right pallidum ($p = .087$ and $p = .036$, respectively, not surviving Bonferroni correction).

3.1.2 Subregional volumetric changes

An overview of the significant subcortical differences when comparing subregional volume of each of 5 subgroups (i.e., the 4th to 8th decade) relative to our youngest decade (i.e., the 3rd decade) can be found in Figures 3-6. Subregional atrophy in the thalamus (Figure 3) was observed starting from the 5th decade for the right thalamus, and starting from the 6th decade for the left thalamus. This atrophy was widespread, leaving only the thalamic head and ventroposterior regions relatively unaffected. For the putamen (Figure 4), atrophy was observed bilaterally starting from the 6th decade and mainly affected the medial and lateral wall. The caudate (Figure 5) showed bilateral age-related subregional atrophy as well as expansion, starting from the 6th decade. The atrophy mainly affected the medial and lateral wall, whereas expansion was mainly observed in the ventral and dorsal wall. Finally, the pallidum (Figure 6) showed expansion when comparing the 6th decade to the 3rd decade, located in medial parts of the left and right body, and posterior and anterolateral parts of the right body only, followed by bilateral atrophy starting from the 7th decade.

3.2 Age-related bimanual performance declines

Based on inspection of the z-scores, no outliers were found for the Purdue Pegboard Test. Figure 7 shows the relation between age and bimanual performance on the Purdue Pegboard Test. There was a significant negative relation between age and average number of pairs inserted ($r = -.670$, $p < .001$), indicating that bimanual performance deteriorated with increasing age.

3.3 Relation between age-related subcortical atrophy and bimanual performance decline

3.3.1 Potentially mediating structures

Partial Pearson correlations were used to explore in which structures variation in corrected global volume was related to bimanual performance, independent of age. None of these partial correlations reached significance. Therefore, global volumes were not included in the mediation models.

3.3.2 Potentially mediating subregions of structures

The GLM (FSL) was used to correlate subregional volume of the subcortical structures with bimanual performance, controlling for the effect of age. We found significant partial correlations between volumes of the ventral and lateral part of the body of the left thalamus, and the ventrolateral part of the body of the right thalamus, and bimanual performance (Figure 8, left side). Therefore, these thalamic subregions were selected as potentially mediating subregions in the relation between age and bimanual performance. Based on the Oxford Thalamic Connectivity Probability Atlas, thresholded at 25% of the maximum connectivity count (Johansen-Berg et al., 2005), both clusters in the left thalamus as well as the cluster in the right thalamus corresponded with the thalamic connectivity profile to the premotor areas, and primary motor and somatosensory cortices (Figure 8, right side). None of the other subcortical structures showed subregional partial correlations with bimanual performance.

3.3.3 Mediation analyses

We conducted mediation analyses to determine whether the effect of age on bimanual performance could be explained by age-related atrophy of subcortical structures. Based on the results of the mediator selection procedures, three thalamic subregions were tested for significant mediation in separate mediation models (see Figure 8, left side): The first and second model included volume of the ventral and the lateral part of the left thalamic body, respectively, the third model included volume of the ventrolateral part of the right thalamic body. The total effect of age on bimanual performance ($c \pm$ SEM) was -0.067 ± 0.008. This implies that, similar to what we described above, higher age is associated with lower performance on the bimanual Purdue Pegboard Test. Including volume of the potential mediating subregions in 3 separate mediation models, this total effect of age was separated into direct (c') and indirect ($a*b$) effects as shown in Table 3. The effect of age on bimanual performance was shown to be partly mediated by volume of all three thalamic subregions (as indicated by the significant indirect effects of age): higher age was associated with lower volume measures (indicative of atrophy) in these thalamic subregions, and this atrophy partly accounted for the observed declines in bimanual performance.

4. Discussion

The main aim of the current study was to determine the role of age-related subcortical changes in sensorimotor performance declines. We employed shape analyses of selected subcortical structures (i.e., left and right thalamus, putamen, caudate and pallidum), to provide a detailed overview of the location of age-related deformations of these structures, indicative of subregional volume changes, in addition to the assessment of the global volume of each structure. Furthermore, by means of mediation analyses, we showed that the observed performance declines with increasing age were accounted for by atrophy in left and right thalamic subregions that subserved specific connections with the premotor, primary motor and somatosensory cortical areas.

4.1 Global and subregional subcortical volumetric changes across the adult lifespan

We first investigated linear relations between age and global volume (corrected for TIV) of the selected subcortical structures across the adult lifespan. Significant negative correlations, indicative of age-related atrophy, were found in the bilateral thalamus, putamen and caudate, but not in the pallidum. The observed atrophy with increasing age in the thalamus, putamen and caudate is generally in line with accumulating evidence from previous cross-sectional studies (Cherubini et al., 2009; Fjell et al., 2013 (not caudate); Goodro et al., 2012; Greenberg et al., 2008; Gunning-Dixon et al., 1998; Hasan, Halphen, Boska, & Narayana, 2008; Hughes et al., 2012; Inano et al., 2013 (not caudate); Jancke et al., 2014; Krishnan et al., 1990; Li et al., 2014 (not caudate); Long et al., 2012; Luft et al., 1999; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004; Van Der Werf et al., 2001; Walhovd et al., 2005; Walhovd et al., 2011; Xu et al., 2000) and longitudinal studies (Fjell et al., 2013; Raz et al., 2005; Raz et al., 2003). Findings with respect to pallidal volumetric changes during aging have been less consistent. Our finding, indicating lack of significant volume declines, is in line with several previous studies (Cherubini et al., 2009; Gunning-Dixon et al., 1998; Inano et al., 2013; Jernigan et al., 2001; Luft et al., 1999; Raz et al., 2003; Walhovd et al., 2005), but in contrast to other studies reporting age-related pallidal atrophy (Fjell et al., 2013; Goodro et al., 2012; Jancke et al., 2014; Jiang et al., 2014 (only in left pallidum); Li et al., 2014 (only trendwise); Long et al., 2012; Walhovd et al., 2011). These diverging results are likely due to heterogeneity in participant samples, segmentation approaches, region of interest definitions, and statistical corrections and thresholding.

To gain more insight into the location of these age-related volumetric changes, we additionally performed shape analyses to enable subregional volume assessment. To the best of our knowledge, we are the first to use shape analyses for this selection of structures across the lifespan to present a detailed overview of the age-related subregional differences. This was achieved by comparing shapes of participants of each of 5 subgroups (4th to 8th decade) to those of the youngest participants (3rd decade). A widespread pattern of subregional atrophy with increasing age (inward deformations) in all

structures was detected. Surprisingly, along with subregional atrophy in all structures, the shape analyses also revealed subregional expansion (outward deformations) associated with increasing age in the bilateral caudate and pallidum. Although this may appear counterintuitive at first sight, several potential explanations can be put forward. First, our result of caudatal expansion in older adults is consistent with previous reports (Fjell et al., 2013; Goodro et al., 2012; Lemaitre et al., 2005; Long et al., 2012; Walhovd et al., 2011). Second, identification of subtle age-related subregional expansion in a structure that also undergoes subregional atrophy represents an important added value of the shape analyses approach as compared to global volume analyses. Accordingly, the identification of age-related expansion as well as atrophy in the pallidum using shape analyses might explain why no relation was found between global pallidal volume and age in the current study. Interestingly, previous studies that observed age-related expansion similar to ours interpreted their findings as possibly due to an artifact (Lemaitre et al., 2005), image processing methodology (Long et al., 2012), and inaccurate registration (Goodro et al., 2012). However, the accumulating evidence of regional age-related expansion suggests that these findings could reflect genuine changes, which definitely require further investigation. A possible working hypothesis could be that subregional expansion is indirectly related to compensatory mechanisms or changes in performance strategy that are implemented by older adults to cope with the emerging structural brain changes (Cabeza & Dennis, 2013; Goble et al., 2010; Heuninckx, Wenderoth, & Swinnen, 2008). However, this goes beyond the scope of the present paper.

4.2 Subregional thalamic atrophy accounts for bimanual performance declines with increasing age across the adult lifespan

As expected, we observed bimanual performance declines with increasing age across the adult lifespan. To explore the role of subcortical volumetric changes in these age-related performance declines, we employed recently developed mediation analyses (Hayes, 2012). Using corrected global volume measures, no mediation effects were found, indicating that global volume approaches may not be sensitive enough to identify biomarkers of subcortical aging related to sensorimotor performance declines.

Using subregional volume measures, age-related atrophy of the ventral and lateral part of the body of the left thalamus, and the ventrolateral part of the body of the right thalamus was shown to partly explain the observed bimanual performance declines with increasing age. The thalamus is a central relay station, receiving input from the cortex via cortico-striatal connections, and ultimately projecting back to the prefrontal, premotor, primary, sensory, occipital, posterior parietal and temporal cortices through thalamocortical pathways (Alexander et al., 1986; Behrens et al., 2003; Hoover & Strick, 1993). Because of this functional topography, it was expected that atrophy of specific subregions, connected with cortical regions relevant for sensorimotor performance, would mediate age-related

bimanual performance declines. Indeed, these thalamic subregions corresponded with the thalamic connectivity profile to the premotor, primary motor and somatosensory areas (Johansen-Berg et al., 2005), which are known to play a crucial role in bimanual coordination (Cardoso de Oliveira, 2002; Swinnen & Wenderoth, 2004).

In the current study, we tested the very specific hypothesis that age-related atrophy of subregions of the bilateral thalamus, putamen, caudate and pallidum, which are connected with cortical regions involved in motor control, accounts for age-related bimanual performance declines. This hypothesis was mainly motivated by results from previous studies implying the importance of these structures and their connections in bimanual coordination. Our findings highlight the importance of age-related deterioration in specific parts of the thalamocortical functional circuit in accounting for sensorimotor performance declines. However, as a result of this focused analysis, we can neither make any statements about the possible contribution of atrophy in the investigated structures to performance on other tasks, nor about the impact of atrophy in other brain regions to the observed bimanual declines. Nevertheless, our findings offer opportunities for future research directed at identifying localized patterns of atrophy that may serve as biomarkers of healthy brain aging, possibly underlying behavioral declines in multiple domains.

5. Conclusion

The role of age-related subcortical changes in bimanual performance declines was investigated using recently developed subregional volume measures in addition to the more conventional global volume indices. Widespread age-related global as well as subregional volumetric changes were found. Furthermore, mediation analyses indicated that the observed age-related bimanual performance declines could partly be explained by atrophy in left and right thalamic subregions, specifically subserving connections with the premotor, primary motor and somatosensory areas. Our findings suggest that subregional volume assessments by means of shape analyses serve as a sensitive tool with high spatial resolution to reveal distinct age-related brain-behavior associations, which can easily go unnoticed with global volume measures.

Disclosure statement

All authors report no disclosures relevant to the manuscript.

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7. Tables

Table 1. Sizes and age ranges of the different decades.

Decade	N (F/M)	Age range (years)
3rd	20 (11/9)	20-29
4th	11 (6/5)	30-39
5th	12 (6/6)	40-49
6th	16 (8/8)	50-59
7th	17 (8/9)	60-69
8th	15 (6/9)	70-79

Note: N: number of participants; F: females, M: males

Table 2. Descriptive statistics of uncorrected global volume and global volume corrected for total intracranial volume of the subcortical structures, and Pearson correlations of corrected global volume with age.

Subcortical structure	Global volume (mm^3) ± SEM		Corrected global volume ± SEM		$r_{\text{corrected global volume. age}}$	
	Left	Right	Left	Right	Left	Right
Thalamus	8079.80 ± 86.17	7915.72 ± 88.22	5.27 ± 0.05	5.16 ± 0.05	-.587 ***	-.628 ***
Caudate	3474.16 ± 46.34	3607.35 ± 49.67	2.27 ± 0.03	2.35 ± 0.03	-.526 ***	-.481 ***
Putamen	4965.99 ± 64.03	5051.50 ± 67.58	3.24 ± 0.04	3.30 ± 0.04	-.583 ***	-.655 ***
Pallidum	1854.77 ± 24.02	1862.15 ± 22.84	1.21 ± 0.01	1.21 ± 0.01	-.181 *ns*	-.220 *ns*

Note: SEM, standard error of the mean; *r* = Pearson correlation. ******* $p < .001$, *ns* = not significant.

Table 3: Overview of the mediation analyses using potentially mediating subregions of structures based on subregional volume measures.

Subregion	**Direct effect of age** *c' (SEM)*	**Indirect effect of age** *a*b (95% bootCI)*	**Mediation effect size** R^2_{med} *(95% bootCI)*
Left thalamus			
Ventral part of the body	**-0.052** (0.009) ***	**-0.014** (-0.027 -0.006)	**.24** (.13 .36)
Lateral part of the body	**-0.041** (0.011) ***	**-0.026** (-0.043 -0.010)	**.37** (.25 .50)
Right thalamus			
Ventrolateral part of the body	**-0.048** (0.001) ***	**-0.018** (-0.035 -0.005)	**.30** (.18 .42)

Note: *c'*= direct effect of age on bimanual performance; *SEM* = standard error of the mean; *a*b* = indirect effect of age on bimanual performance through subregional volume; *95% bootCI* = 95% bias-corrected bootstrap confidence interval; R^2_{med} = the proportion of variance in bimanual performance attributable to the mediation effect; *** $p < .001$.

8. Figures

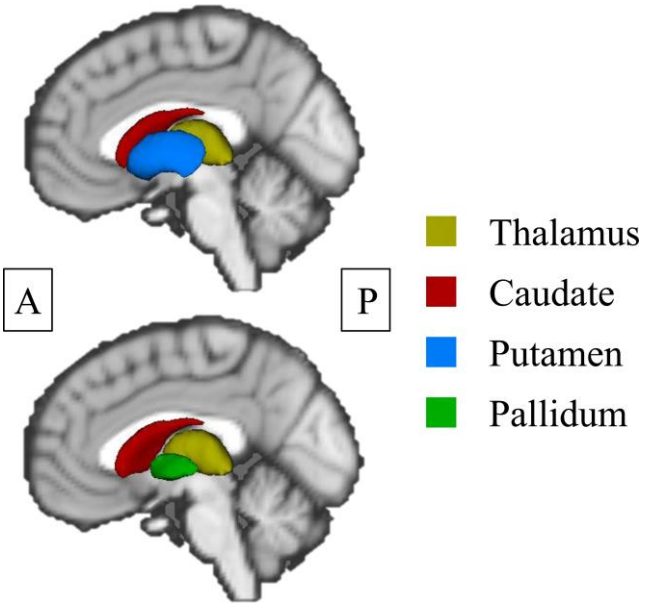

Fig. 1. **FIRST segmentation of left and right thalamus, caudate, putamen and pallidum.** The left side is shown here. In the bottom figure, the putamen has been removed to reveal the pallidum. A = anterior; P = posterior.

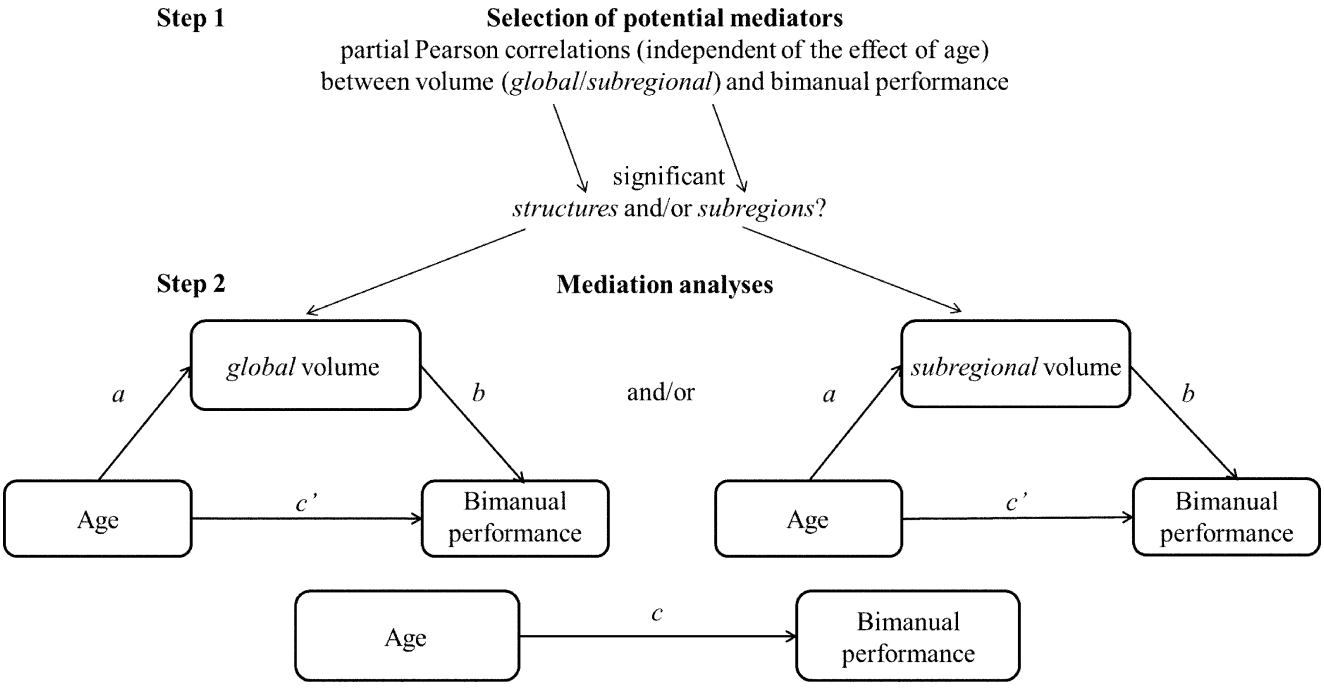

Fig. 2. **Overview of the mediation analyses. Step 1:** partial Pearson correlations (independent of the effect of age) were used to select the potentially mediating structures and/or subregions. **Step 2:** mediation models with age modeled to affect bimanual performance directly, as well as indirectly through corrected global volume and/or subregional volume of the selected potentially mediating

structures and subregions of a structure, respectively. *a* = the effect of age on the potential mediator; *b* = the effect of the potential mediator on bimanual performance controlling for age; *c'*= direct effect of age on bimanual performance, controlling for the indirect effect *a*b*; *c* = total effect of age on bimanual performance.

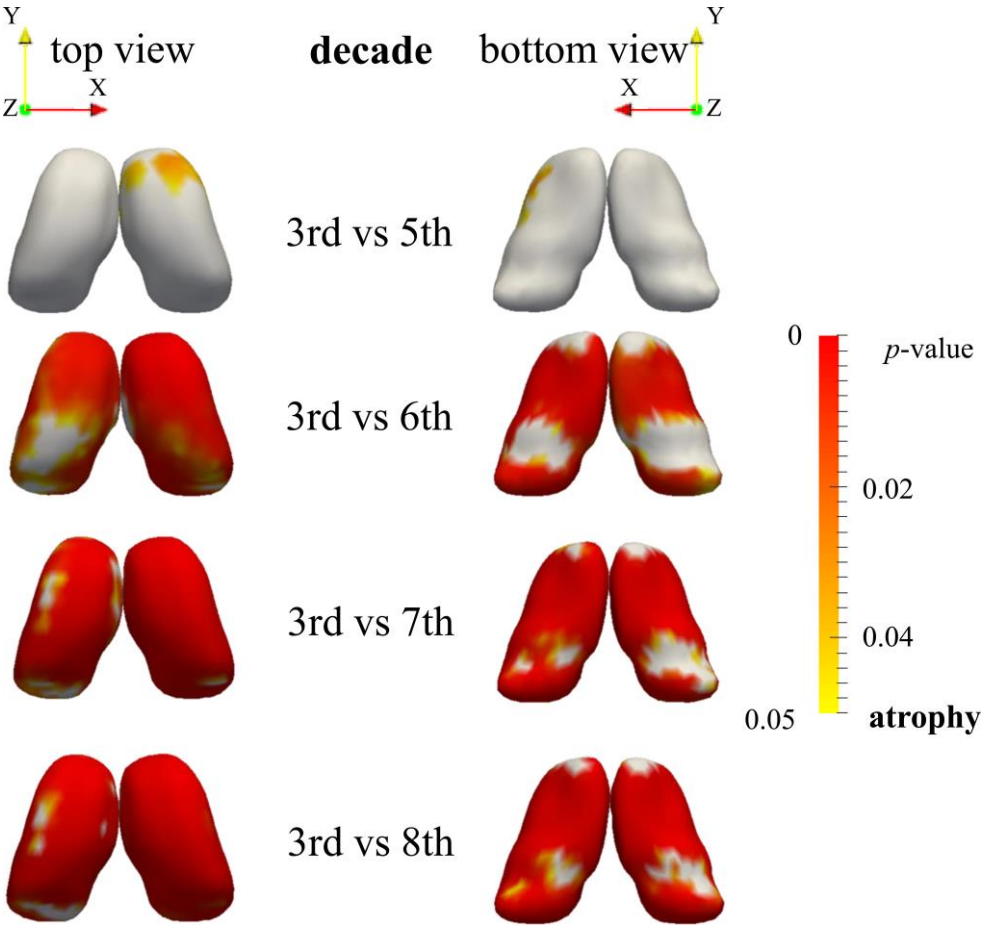

Fig. 3. **Thalamus.** Vertex-wise comparisons of thalamus. Age-related atrophy was observed starting from the 5th decade for the right thalamus, and starting from the 6th decade for the left thalamus. X = right; Y = front; Z = top.

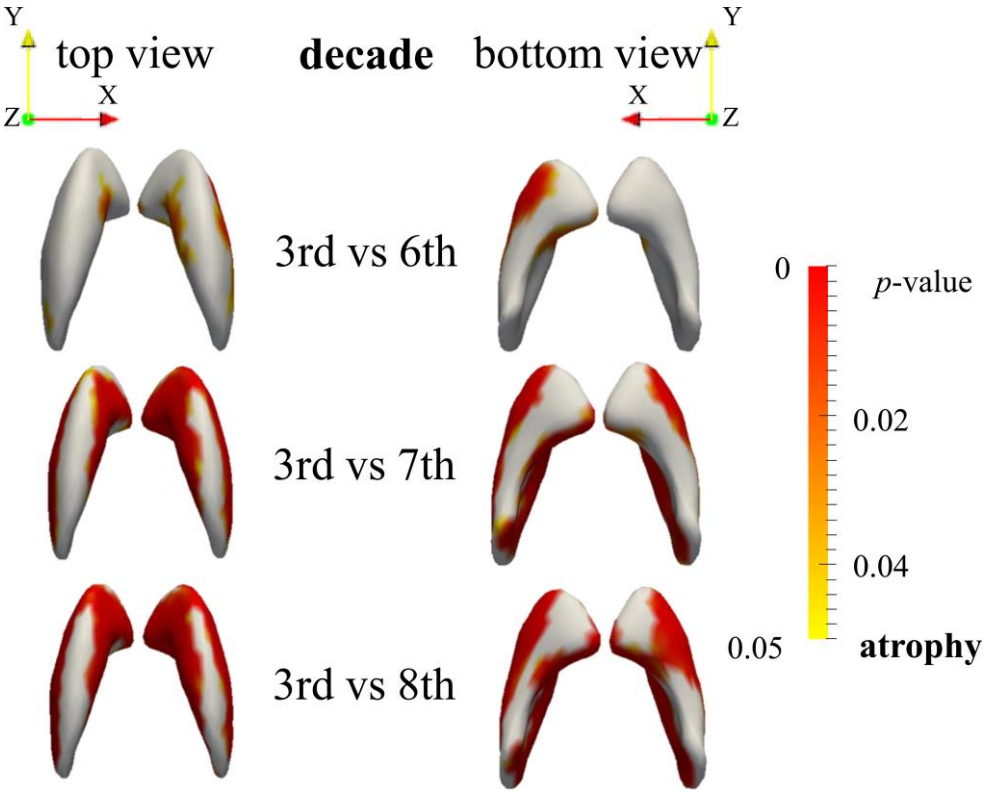

Fig. 4. **Putamen.** Vertex-wise comparisons of putamen. Age-related subregional atrophy was observed bilaterally starting from the 6th decade. X = right; Y = front; Z = top.

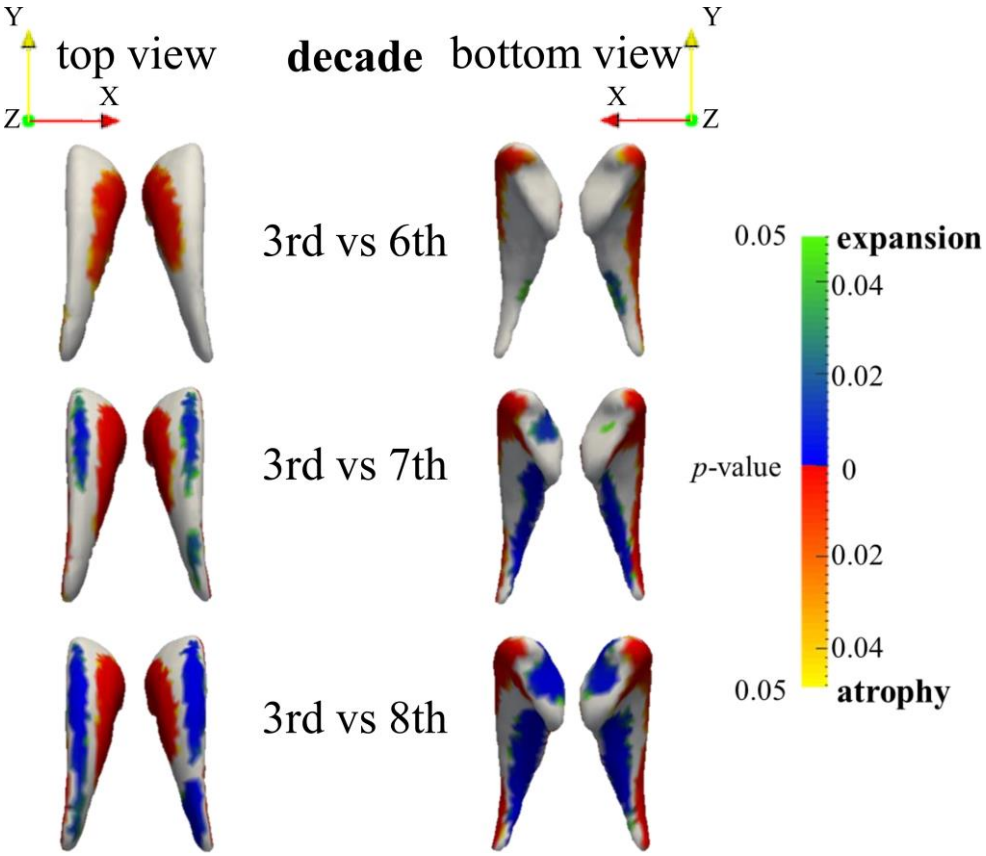

Fig. 5. **Caudate.** Vertex-wise comparisons of caudate. Age-related subregional atrophy as well as expansion was observed starting from the 6th decade. X = right; Y = front; Z = top.

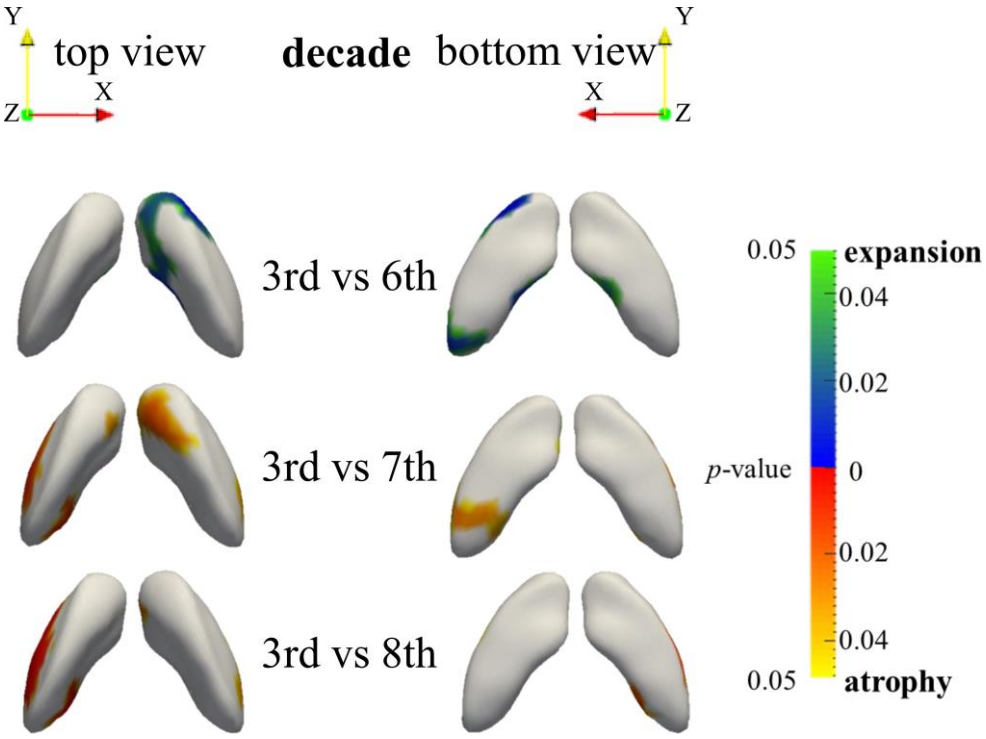

Fig. 6. **Pallidum.** Vertex-wise comparisons of pallidum. Subregional expansion was observed when comparing the 6th decade to the 3rd decade. Age-related subregional atrophy was observed starting from the 7th decade. X = right; Y = front; Z = top.

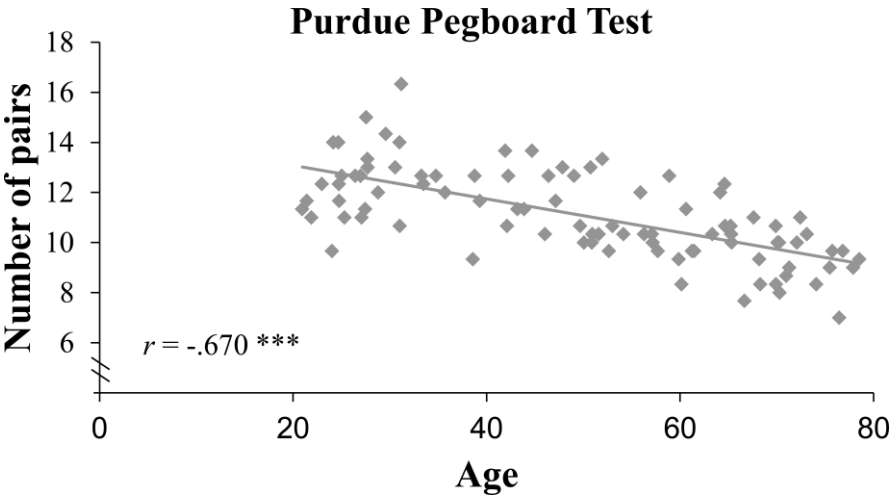

Fig. 7. **Scatter plot indicating the relationship between age and bimanual performance on the Purdue Pegboard Test.** *** $p < .001$.

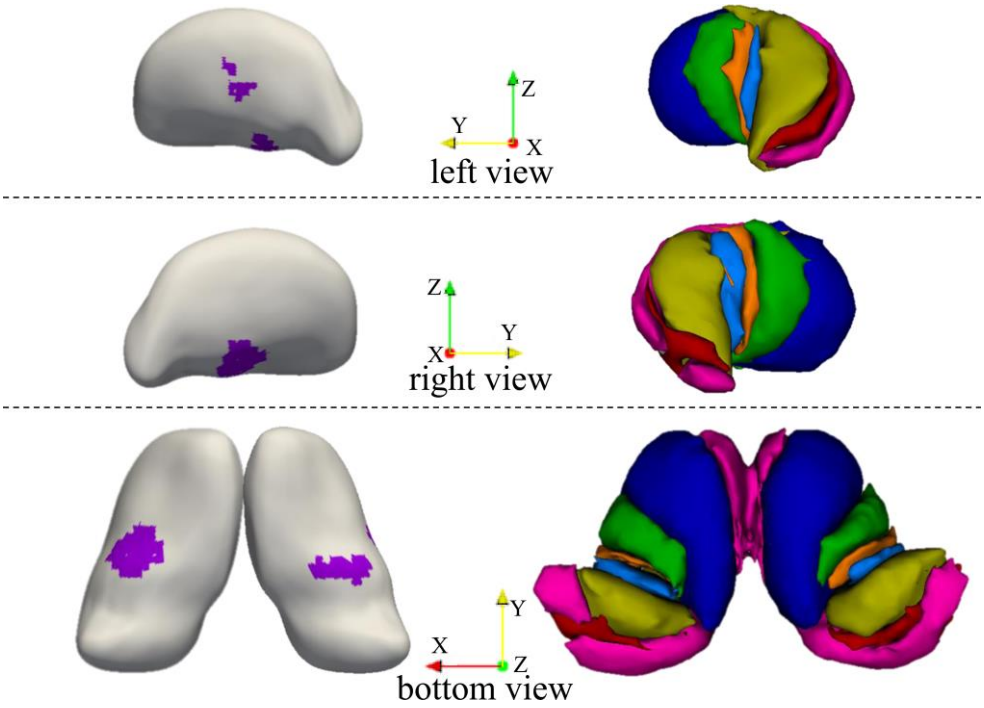

Fig. 8. **Left side: thalamic clusters (purple) selected as potentially mediating subregions in the relation between age and bimanual performance.** Reduced volumes of these thalamic subregions showed a relation with lower bimanual performance, independent of the effect of age. X = right; Y = front; Z = top. **Right side: the oxford Thalamic Connectivity Probability Atlas shows the connectivity profile of the thalamus.** Blue = prefrontal cortex; green = premotor cortex; orange = primary motor cortex; light blue = sensory cortex; red = occipital cortex; yellow = posterior parietal cortex; pink = temporal cortex (Johansen-Berg et al., 2005).